Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results

CaRESS Steering Committee

Objective: **Current clinical trials evaluating carotid stenting have focused on high-risk patients and may not reflect the broad population of patients with carotid stenosis who undergo treatment to prevent stroke. The Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I study is a multicenter, prospective, nonrandomized trial designed to address the question of whether carotid stenting (CAS) with cerebral protection is comparable to carotid endarterectomy (CEA) in patients with symptomatic and asymptomatic carotid stenosis.**

Methods: **Patients with symptomatic (with >50% stenosis) or asymptomatic (with >75% stenosis) carotid stenosis were entered into the study in a 2:1 ratio of carotid stent and GuardWire Plus distal protection device. This unique trial model was developed through collaboration with the International Society of Endovascular Specialists, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, the National Institutes of Health, and industry representatives. The primary end points included death and stroke at 30 days and a composite 1-year end point of death, stroke, or myocardial infarction (MI) from 0 to 30 days and death or stroke from 31 days to 1 year. The secondary end points included residual stenosis, restenosis, repeat angiography, and carotid revascularization at 30 days and 1 year and quality-of-life changes at 1 year.**

Results: **A total of 397 patients (254 CEA and 143 CAS) were enrolled in the study: 32% were symptomatic and 68% were asymptomatic. There were no significant differences in patient characteristics, symptoms, or surgical risk profiles between groups at baseline. Kaplan-Meier analysis revealed no significant differences in combined death/stroke rates at 30 days (3.6% CEA vs 2.1% CAS) or at 1 year (13.6% CEA vs 10.0% CAS). Similarly, there was no significant difference in the combined end point of death, stroke, or MI at 30 days (4.4% CEA vs 2.1% CAS) or at 1 year (14.3% CEA vs 10.9% CAS). There were no significant differences between CEA and CAS in the secondary end points of residual stenosis (0% CEA vs 0.9% CAS), restenosis (3.6% CEA vs 6.3% CAS), repeat angiography (2.1% CEA vs 3.6% CAS), carotid revascularization (1.0% CEA vs 1.8% CAS), or change in quality of life (−1.56 points CEA vs −4.22 points CAS).**

Conclusions: **The CaRESS phase I study suggests that the 30-day and 1-year risk of death, stroke, or MI with CAS is equivalent to that with CEA in symptomatic and asymptomatic patients with carotid stenosis. (J Vasc Surg 2005;42: 213-9.)**

In current clinical practice, carotid stenting (CAS) has emerged as a viable alternative for patients who are deemed at high risk for surgery or poor candidates for carotid endarterectomy (CEA), which is considered the standard of care.[1] This is demonstrated by trials such as ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR) (Guidant Corporation, Menlo Park, Calif), Stenting and angioplasty with protection in patients at high risk for endarterectomy trial (SAPPHiRE) (Cordis Corporation, Warren, NJ), Evaluation of the Medtronic AVE self-expandable carotid stent system with distal protection in the treatment of carotid stenosis (MAVEerILC) (Medtronic Vascular, Santa Rosa, Calif), Carotid artery revascularization using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent trial (CABernET) (Boston Scientific/EndoTex, Cupertino, Calif), and Registry study to evaluate the Neuroshield bare wire cerebral protection system and X-Act Stent in patients at high risk for carotid endarterectomy (SECuRITY) (Abbott Vascular, Redwood City, Calif).[2-6] However, there is considerable variability in the definition of high risk among these trials based on inclusion criteria.

Because the recent trials have focused on relatively narrow indications of high-risk patient populations, they are unlikely to answer the overall question of whether CAS with distal, embolic protection is equivalent to the standard of care (ie, CEA) for most patients with carotid stenosis who are at risk for stroke. The two most referenced trials in the current clinical decision-making process for carotid stenosis are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS), in which inclusion for treatment is based on symptoms rather than surgical risk.[7,8] Just as patients undergo open surgical repair (ie, CEA) on the basis of symptoms rather than surgical risk, the safety and efficacy of CAS should not be limited only to a high-risk population. The Carotid Revascularization

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Endarterectomy vs Stent Trial (CREST) funded by the National Institutes of Health uses symptomatology to determine eligibility.[9] Similarly, the Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) trial was designed on the basis of the broad category of standard risk by using symptomatology as a defining criterion for stratification in the study.[10]

CaRESS is a unique trial that developed through early collaboration between the International Society of Endovascular Specialists, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, the National Institutes of Health, and the industry. The 30-day results have been previously published.[10] This article presents the comprehensive 1-year follow-up results of the CaRESS phase I trial.

METHODS

Study design. The CaRESS trial is a multicenter, prospective, nonrandomized equivalence cohort study that was designed to evaluate the safety and effectiveness of CAS with embolic protection compared with CEA in a broad-risk population with symptomatic and asymptomatic carotid stenosis. Outcomes were measured at 30 days and 1 year after the procedure. For purposes of comparison with other published trials, results are also stratified by symptoms and by surgical risk. Lacking a uniform, standard definition of *high risk* for trials such as ARCHeR, SAPPHiRE, MAVErIC, CABernET, or SECuRITY, the definition published by Ouriel et al[11] was used for this article. *High risk* is defined as having any one of the following criteria: (1) age 80 years or older, (2) New York Heart Association class III/IV for congestive heart failure, (3) chronic obstructive pulmonary disease, (4) contralateral stenosis >50%, (5) prior CEA or CAS, or (6) prior coronary artery bypass grafting.[11]

This study was conducted in accordance with the Declaration of Helsinki of 1996, the International Conference on Harmonization guidelines for good clinical practice, and Code of Federal Regulations 21 CFR 812 for Investigational Device Exemptions. This trial was conducted under a Sponsor-Investigator Device Exemption held by the International Society of Endovascular Specialists. The Monorail Wallstent (Boston Scientific Corporation, Natick, Mass) CAS and GuardWire Plus (Medtronic Vascular) distal protection devices were used in the CAS arm in accordance with the instructions for use.[10] Both Boston Scientific Corporation and Medtronic Vascular provided the devices free of charge and fully funded the study.

The CaRESS model was approved by the Food and Drug Administration to allow multiple manufacturers to (1) participate in one clinical trial for a broad-risk population, (2) provide full use of control (CEA) data sets, (3) provide an aggregate CAS data set for additional statistical power, and (4) reduce the burden for an individual manufacturer conducting a similar trial for labeling approval. This model will be implemented in phase II.

Information on study design, clinical site selection, and patient enrollment has been previously published.[10] A summary of the indications for allocation to each study arm and intervention techniques is provided here.

The clinical characteristics of the study patients, including conditions such as diabetes, congestive heart failure, hypercholesterolemia, and coronary artery disease, were entered in the database on the basis of the history and physical examination performed by the physician who provided clearance for the patient to undergo carotid intervention.

The choice of treatment by CAS or CEA was based solely on physician and patient preference. This design more accurately reflects the true clinical environment.

Patients undergoing CAS were previously placed on aspirin and ticlopidine or clopidogrel and heparinized during the procedure to maintain an activated coagulation time between 250 and 300 seconds. After the procedure, these patients were maintained on aspirin (325 mg daily) indefinitely and either clopidogrel or ticlopidine for 4 weeks. Access to the common carotid artery (CCA) with a guide catheter was attained by using the standard techniques of exchanging in the external carotid artery or CCA. The filter wire was deployed above the lesion, and then the wire was used as the platform for all percutaneous devices. The filter was captured at the end of the procedure, and final cervical carotid and intracranial carotid images were obtained.

Patients undergoing CEA were placed on aspirin before the procedure. Additional appropriate medications were prescribed per investigator discretion and institutional procedures. The choice of the specific technique of endarterectomy was left to the treating physician.

End points. The primary end points for the phase I trial included all-cause mortality or stroke within 30 days and 1 year of the procedure. The secondary end points included a composite of 30-day all-cause mortality, stroke, or acute myocardial infarction (AMI) and 1-year all-cause mortality or stroke; residual stenosis, restenosis, repeat angiography, and carotid revascularization at 30 days and 1 year; and quality-of-life changes at 1 year. An independent data and safety monitoring board reviewed the centrally adjudicated clinical events for safety.

Definitions. Stroke was defined as any localized neurological deficit lasting longer than 24 hours as assessed in a standard neurologic examination by a neurologist and either confirmed by a magnetic resonance imaging or head computed tomographic scan or independently confirmed during central adjudication. AMI was defined as any new pathologic changes on electrocardiogram or total creatine kinase 2 or more times the upper limit of normal with an increased myocardial band fraction. Residual stenosis was defined as more than 50% stenosis in the target lesion after the index study procedure. Restenosis was defined as 75% narrowing documented by ultrasonography or symptomatic narrowing greater than 50% that required secondary treatment. The Multidimensional Index of Life Quality (MILQ) questionnaire measured a weighted combination of mental health and social and physical functioning items to evaluate quality of life.[11-13]

Table I. Baseline demographics and clinical characteristics by treatment arm

Variable	*Treatment arm*		P *value*
	CEA (n = 254)	*CAS (n = 143)*	
Demographics			
Age, y (mean ± SD)	71.4 ± 8.8	71.2 ± 9.6	.85
Male sex	161 (63%)	86 (60%)	.52
Caucasian race	236 (93%)	133 (93%)	.97
Height, cm (mean ± SD)	169.6 ± 9.8	170.6 ± 10.3	.07
Weight, kg (mean ± SD)	78.5 ± 16.2	81.9 ± 20.4	.07
Risk factors			
Symptomatic	83 (33%)	44 (31%)	.70
Stenosis diameter			.06
50%-75%	29 (11%)	8 (6%)	
>75%	225 (89%)	135 (94%)	
Medical history			
TIA	69 (27%)	32 (22%)	.29
CVA	41 (16%)	28 (20%)	.39
TIA or CVA	94 (37%)	53 (37%)	.99
CEA before study	29 (11%)	43 (30%)	<.01
Carotid stent before study	0 (0%)	8 (6%)	<.01
Prior peripheral angioplasty	1 (0.4%)	3 (2%)	.14
Contralateral stenosis >50%	100 (40%)*	49 (34%)	.30
CAD or previous AMI	154 (61%)	95 (66%)	.25
Congestive heart failure	42 (17%)	19 (13%)	.39
Hypertension	206 (81%)	116 (81%)	1.00
Hypercholesterolemia	177 (70%)	91 (64%)	.22
Diabetes mellitus	61 (24%)	42 (29%)	.24
Peripheral vascular disease	103 (41%)	65 (45%)	.34

CEA, Carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *TIA,* transient ischemic attack; *CVA,* cerebrovascular accident; *CAD,* coronary artery disease; *AMI,* acute myocardial infarction.
*n = 253 patients.

Statistical analysis. Data were entered into the Advanced Data Entry and Protocol Tracking data management system developed by New England Research Institutes, Inc (Watertown, Mass). All analyses were performed by using SAS (SAS Institute Inc, Cary, NC) and SPSS (SPSS Inc, Chicago, Ill) statistical software. Baseline characteristics of the CEA and CAS patient groups were compared by using the Student *t* test for continuous variables and χ^2 (cell size ≥5) or Fisher exact (cell size <5) tests for categorical data. Multivariable regression analysis using the Cox proportional hazard model was performed to identify baseline predictive factors for the composite end point of 30-day death, stroke, or AMI and 1-year death or stroke. Kaplan-Meier estimates of freedom from events for the primary and secondary end points were determined; the log-rank test was used to compare primary and secondary event rates. Differences were considered significant if $P < .05$. Quality-of-life changes based on the MILQ scores were compared by using a *t* test of the net change (baseline to 1 year) compared with 0.

RESULTS

Patient characteristics. A total of 397 patients (254 CEA and 143 CAS) were enrolled in the study. Of the 254 CEA patients, 33% were symptomatic (vs 67% asymptomatic), and 87% were high risk (vs 13% low risk). Similarly, of the 143 CAS patients, 31% were symptomatic (vs 69% asymptomatic), and 84% were high risk (vs 16% low risk). Overall baseline demographics did not differ between the two treatment arms, as seen in Table I.[10] For purposes of this article, baseline characteristics were also stratified by symptoms (Table II) and surgical risk (Table III), as described by Ouriel et al.[11] The stratified comparisons between treatment groups were also not statistically significant, thus further emphasizing the equivalence of the two treatment arms.

Baseline ultrasound characteristics of target lesions revealed that patients in the CEA arm had statistically significantly more stenosis than those in the CAS arm, as demonstrated by peak systolic velocity (PSV; 302 cm/s CEA vs 202 cm/s CAS; $P < .01$), end-diastolic velocity (100 cm/s CEA vs 61 cm/s CAS; $P < .01$) and internal carotid artery (ICA)/CCA PSV ratio (4.4 CEA vs 3.1 CAS; $P < .01$; Table IV.) The average baseline stenosis was 80% to 89% in the CEA arm vs 70% to 79% in the CAS arm as determined by ultrasonography with PSV, end-diastolic velocity, and the ICA/CCA PSV ratio.[14-17] The average percentage stenosis in the CAS arm as determined by carotid angiography was 82%. Angiography was not required in the CEA arm.

In the CAS arm, the distribution of stent placement was 40 (28%) of 143 in the ICA, 12 (8%) of 143 in the CCA, and 91 (64%) of 143 in both the ICA and CCA. The average stent length was 3.66 ± 0.98 mm (range, 1.9-6.5 mm). Of the 143 CAS procedures, 52% were performed by surgeons, 44% were performed by interventional cardiologists, and 4% were performed by interventional radiologists.

Primary end points. The Kaplan-Meier curves for the primary endpoint of all-cause mortality or stroke at 1-year

Table II. Baseline demographics by treatment arm, stratified by symptomatology

Variable	*CEA*		*CAS*		P *value**
	Symptomatic (n = 84)	*Asymptomatic (n = 170)*	*Symptomatic (n = 44)*	*Asymptomatic (n = 99)*	
Age, y (mean ± SD)	70.4 ± 9.2	71.9 ± 8.6	68.9 ± 9.2	72.2 ± 9.7	.14
% Male	61%	65%	61%	60%	.52
% Caucasian	92%	94%	91%	94%	.99
Height, cm (mean ± SD)	168.0 ± 8.6	170.4 ± 9.4	171.5 ± 9.1	170.3 ± 10.5	.21
Weight, kg (mean ± SD)	77.7 ± 18.4	79.0 ± 15.0	84.3 ± 19.5	80.9 ± 20.9	.20
Hypertension	77%	83%	77%	83%	.98
Diabetes mellitus	25%	24%	25%	31%	.26
Hypercholesterolemia	77%	73%	68%	69%	.27
Congestive heart failure	12%	19%	7%	17%	.42
CAD or previous MI	63%	64%	57%	74%	.31

CEA, Carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *CAD,* coronary artery disease; *AMI,* myocardial infarction.
*The *P* value for categorical variables is a Cochran-Mantel-Haenszel χ^2 *P* value for stratified variables. The *P* value for continuous variables is the overall *P* value from an analysis of variance with symptomatology, procedure, and the interaction as factors.

Table III. Baseline demographics by treatment arm, stratified by surgical risk

Variable	*CEA*		*CAS*		P *value**
	High risk (n = 220)	*Low risk (n = 34)*	*High risk (n = 120)*	*Low risk (n = 23)*	
Age, y (mean ± SD)	71.6 ± 9.1	70.3 ± 6.7	71.8 ± 9.8	68.3 ± 8.3	.34
% Male	64%	59%	62%	52%	.55
% Caucasian	94%	88%	92%	100%	.97
Height, cm (mean ± SD)	169.6 ± 9.3	169.6 ± 8.9	170.8 ± 10.3	169.9 ± 8.9	.78
Weight, kg (mean ± SD)	78.8 ± 16.1	77.2 ± 16.8	82.4 ± 20.9	79.6 ± 18.1	.27
Hypertension	81%	82%	80%	87%	.98
Diabetes mellitus	22%	41%	30%	26%	.28
Hypercholesterolemia	74%	79%	71%	60%	.27
Congestive heart failure	17%	12%	13%	17%	.44
CAD or previous MI	63%	67%	71%	57%	.29

CEA, Carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *CAD,* coronary artery disease; *AMI,* myocardial infarction.
*The *P* value for categorical variables is a Cochran-Mantel-Haenszel χ^2 *P* value for stratified variables. The *P* value for continuous variables is the overall *P* value from an analysis of variance with symptomatology, procedure, and the interaction as factors.

Table IV. Baseline ultrasound lesion characteristics between treatment arms

Variable	*CEA*	*CAS*	P *value*
PSV (mean ± SD)	302 ± 122 cm/s	202 ± 147 cm/s	<.01
End-diastolic velocity (mean ± SD)	100 ± 50 cm/s	61 ± 53 cm/s	<.01
ICA/CCA PSV ratio (mean ± SD)	4.4 ± 2.3	3.1 ± 2.8	<.01

CEA, Carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *PSV,* peak systolic velocity; *ICA,* internal carotid artery; *CCA,* common carotid artery.

demonstrate no statistically significant differences between curves (Fig 1). Although the CAS rates were consistently lower than the CEA rates, the most notable difference was in stroke rates (30 days: 3.6% CEA vs 2.1% CAS, not significant; 1 year: 9.8% CEA vs 5.5% CAS, not significant), which dominated all the combined rates. The death rates remained comparable across both treatment arms (30 days: 0.4% CEA vs 0.0% CAS, not significant; 1 year: 6.6% CEA vs 6.3% CAS, not significant). The lack of statistical significance is probably due to the lack of numbers in this preliminary database. Kaplan-Meier estimates for the end points of all-cause mortality, stroke, or AMI at 30 days (Table V) showed little change compared with the primary end points at 1 year (Table VI). Seven cases of AMI were observed: five (2.4%) in the CEA arm and two (1.7%) in the CAS group. Two of the five AMIs in the CEA group occurred within 30 days of the index procedure (Fig 1).

When adjusted for baseline predictions by using the Cox proportional hazard regression, the treatment arm differences at 1 year (Table VII) remained. Hazard ratios less than 1 (treatment, CAS vs CEA) indicated that, controlling for all other covariates, there was a lower risk of the composite 1-year primary end point in the CAS arm. Hazard ratios greater than 1 (for example, age) indicated that, controlling for all other covariates, there was a greater risk of the composite 1-year primary end point as age increased. Multivariate analysis did not show significant baseline predictors of outcome other than age (odds ratio, 1.056; $P = .0069$) and prior carotid

Table V. Kaplan-Meier estimates of event rates at 30 days for primary end points

	All-cause mortality		*Stroke*		*AMI*		*Combined death/stroke*		*Combined death/stroke/AMI*	
Variable	*CEA*	*CAS*	*CEA*	*CAS*	*CEA*	*CAS*	*CEA*	*CAS*	*CEA*	*CAS*
No. at risk	254	143	254	143	254	143	254	143	254	143
No. events	1	0	9	3	2	0	9	3	11	3
No. censored*	26	6	24	5	27	6	24	5	24	5
K-M estimate	0.9957	1.0000	0.9639	0.9786	0.9921	1.0000	0.9639	0.9786	0.9560	0.9786
SE	0.00425	0.0000	0.0118	0.0122	0.00555	0.0000	0.0118	0.0122	0.0130	0.0122
Event rate†	0.4%	0.0%	3.6%	2.1%	0.8%	0.0%	3.6%	2.1%	4.4%	2.1%
P value	.445		.408		.291		.408		.241	

AMI, Acute myocardial infarction; *CEA,* carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *K-M,* Kaplan-Meier.
*The number censored includes patients who either terminated before the 30-day follow-up or for whom specific 30-day data were not obtained even though the patient completed the visit or remained enrolled in the study.
†Calculated as (1 − K-M estimate), this represents a person-year rate.

Table VI. Kaplan-Meier estimates of event rates at 1 year for primary end points

	All-cause mortality		*Stroke*		*AMI*		*Combined death/stroke*		*Combined death/stroke/AMI*	
Variable	*CEA*	*CAS*	*CEA*	*CAS*	*CEA*	*CAS*	*CEA*	*CAS*	*CEA*	*CAS*
No. at risk	254	143	254	143	254	143	254	143	254	143
No. events	14	8	22	7	5	2	30	13	32	14
No. censored*	108	49	106	53	119	59	98	47	98	47
K-M estimate	0.9337	0.9373	0.9018	0.9450	0.9763	0.9826	0.8643	0.8998	0.8568	0.8910
SE	0.0172	0.0215	0.0201	0.0204	0.0107	0.0122	0.0233	0.0265	0.0237	0.0277
Event rate†	6.6%	6.3%	9.8%	5.5%	2.4%	1.7%	13.6%	10.0%	14.3%	10.9%
P value	.893		.133		.619		.302		.288	

AMI, Acute myocardial infarction; *CEA,* carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *K-M,* Kaplan-Meier.
*The number censored includes patients who either terminated before the 1-year follow-up or for whom specific 1-year data were not obtained even though the patient completed the visit or remained enrolled in the study.
†Calculated as (1 − K-M estimate), this represents a person-year rate.

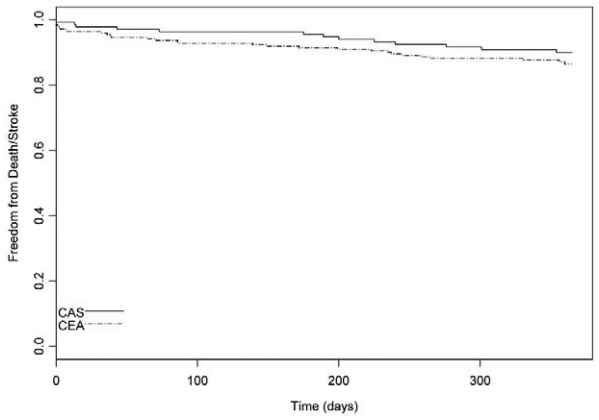

Fig 1. Kaplan-Meier curves at 1 year for combined death/stroke. *CAS,* Carotid stenting; *CEA,* carotid endarterectomy.

intervention (odds ratio, 2.786; $P = .0025$), as demonstrated in Table VII for the 1-year composite end point. Other factors, such as sex, race, surgical risk, symptomatology, prior transient ischemic attack or stroke, or percentage stenosis, were not statistically significant predictors of the primary end points.

Table VII. Cox proportional hazard regression of baseline predictive factors for the composite end point of death, stroke, or myocardial infarction at 0 to 30 days plus death or stroke at 31 days to 1 year (analysis of maximum likelihood estimates)

Variable	*Hazard ratio*	*95% Hazard ratio confidence limits*	P *value*
CAS vs CEA	0.552	0.276-1.101	.0917
Age	1.056	1.015-1.098	.0069
Female	1.755	0.950-3.244	.0726
Non-Caucasian	1.050	0.318-3.465	.9365
Symptomatology	1.264	0.568-2.815	.5660
Risk	1.915	0.581-6.312	.2857
% Stenosis	1.165	0.375-3.624	.7916
Prior TIA or CVA	1.334	0.645-2.759	.4365
Prior carotid procedures	2.786	1.433-5.419	.0025

CEA, Carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection); *TIA,* transient ischemic attack; *CVA,* cerebrovascular accident.

Secondary end points. The 1-year event rates observed for secondary end points are summarized in Table VIII. The CAS arm had consistently higher rates of residual stenosis (0.9% CAS vs 0% CEA), restenosis (6.3% CAS vs 3.6% CEA),

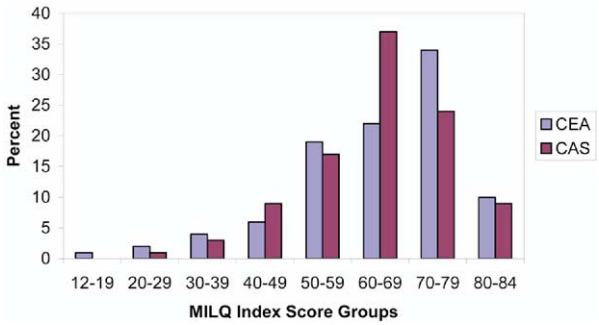

Fig 2. Baseline distribution (percentage) of Multidimensional Index of Life Quality *(MILQ)* scores by treatment group. *CAS,* Carotid stenting; *CEA,* carotid endarterectomy.

repeat angiography (3.6% CAS vs 2.1% CEA), and carotid revascularization (1.8% CAS vs 1.0% CEA), but, as anticipated, none was statistically significant, given the small numbers of prior procedures reported.

The changes in quality of life between baseline and 1 year were also evaluated by using the MILQ scores. Figure 2 shows the baseline distributions of MILQ scores (possible range, 12-84) for each treatment arm. The wide range of scores reflects the broad range of patients recruited into the study. However, there was no statistically significant difference in baseline scores between treatment groups (66 points in the CEA group vs 64 points in the CAS group). There were 191 patients (119 CEA and 72 CAS) with MILQ scores at both baseline and 1 year. Scores were imputed for 16 patients who died before the 1-year visit. In addition, whereas the CAS arm experienced a greater decline in quality of life (−4.22 points CAS vs −1.56 points CEA; $P = .319$), it was not statistically significant.

DISCUSSION

The CaRESS study was initiated to address the utility of CAS with embolic protection for treating carotid artery occlusive disease in current clinical practice. An essential premise of CaRESS is that the evaluation of the safety and efficacy of CAS compared with CEA should not be limited to a high-risk population.

The overall baseline characteristics were remarkably homogenous between treatment groups, with the exception that the CAS arm had more patients who had previous carotid intervention, which was expected.[18] It is noteworthy that, when adjusted for risk or symptomatology, there was still no statistically significant difference in baseline characteristics. This suggests reasonable equivalence in the non–randomly assigned treatment arms.

When compared with the 30-day event rates summarized in Table V, the trend toward longer event-free survival in the CAS arm at 1 year (Table VI) for the primary end points reported here may be artifactual in this phase I study, but it is interesting nonetheless. This trend is particularly noteworthy given the significant effect (hazard ratio) in the opposite direction for prior carotid procedures (Table VII). Rather than indicating that the CAS group is sicker than the CEA group at baseline, the higher prior intervention rate in the CAS group may, indeed, be an indicator of their relative health. They may be more likely to be considered for multiple procedures if their risk is perceived to be adequately low.

Table VIII. Person-year rates at 1-year follow-up for additional end points by treatment arm

Variable	*CEA*	*CAS*	P *value*
Restenosis	7/192 (3.6%)	7/111 (6.3%)	.296
Residual stenosis	0/192 (0.0%)	1/111 (0.9%)	.366
Carotid revascularization	2/192 (1.0%)	2/112 (1.8%)	.627
Repeat angiography	4/192 (2.1%)	4/112 (3.6%)	.472

CEA, Carotid endarterectomy; *CAS,* carotid stenting systems (with cerebral protection).

The composite 1-year rates observed in CaRESS were comparable to the rates observed in the ARCHeR, SAPPHiRE, MAVErIC, and CABernET studies.[2-5] The somewhat higher stroke rates than those reported for NASCET[7] and ACAS[8] may reflect different diagnostic criteria and the lack of rigorous eligibility criteria typical of most randomized trials. Certainly, the plan to include in CaRESS a broad profile of patients typically offered CAS or CEA seems to have been successful in the sense that outcome rates were not lower than those reported by comparable studies, despite the inclusion of a majority of asymptomatic patients.

Despite the potential for bias in the mean MILQ scores, it is noteworthy that the treatment group comparison at 1 year was not statistically significant ($P = .319$) and that baseline scores were comparable. The MILQ scores thus reaffirm the broad patient representation.

The CaRESS study is the only study conducted thus far that attempts to imitate the true clinical environment. In this population of both low- and high-risk patients, the 30-day composite morbidity and mortality rates of 4.4% for CEA and 2.1% for CAS compare well with both NASCET and ACAS. Furthermore, CaRESS compares favorably with the already published high-risk registries or trials using distal protection in which the major adverse event rates at 30 days were 3.8% to 8.2% (ARCHeR, Boston Scientific EPI. A carotid stenting trial for high-risk surgical patients (BEACH), CABernET, MAVErIC, and SAPPHiRE). The most easily compared high-risk trial, SAPPHiRE, had 30-day major adverse event rates of 12.6% for CEA and 5.8% for CAS. The cumulative 1-year major adverse event rates in SAPPHiRE were 20.1% for CEA and 12.2% for CAS; those in CaRESS were 14.3% vs 10.9%, respectively. Although we await the results of the CREST trial as a randomized, prospective study on which to base clinical decisions between CAS and CEA, the CaRESS trial likely reflects more accurately the true decision-making process that will occur when CAS is eventually approved by the Centers for Medicare and Medicaid Services. The CaRESS phase II trial will be able to provide adequate sample size and power to demonstrate equivalence between the two treatment arms.

CONCLUSION

The CaRESS phase I study suggests that the risk of death or stroke 1 year after CAS by using distal protection is equivalent to that after CEA in a broad-category population with carotid stenosis. The CaRESS phase 1 study was able to closely resemble clinical practice by enrolling patients on the basis of the degree of carotid stenosis and symptomatology rather than surgical risk. This uniquely designed trial allows multiple CAS manufacturers to participate and use the resulting data for a broad-risk premarket application submission. As such, CaRESS phase II will be able to establish the precedent of commercialization based on a definablesymptomatology rather than a variable surgical risk definition. Funding for CaRESS phase II is pending.

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APPENDIX

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Members. John Bergan, MD, University of California, San Diego, La Jolla, Calif; Stanley Cohen, MD, Cedars-Sinai Medical Center, Los Angeles, Calif; and O. Dale Williams, PhD, University of Alabama, Birmingham, Ala.

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